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Stroke prevention in Patients with Atrial Fibrillation and Chronic Hepatic Disease

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Orientado por:

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Abstract

Stroke prevention in Patients with Atrial Fibrillation and Chronic Hepatic Disease - Review

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Introduction: Atrial fibrillation is a common cardiac arrhythmia and a major cause of ischaemic stroke. Stroke risk can be accessed using scores like $CHA_2DS_2VAS_c$ and thromboprophylatic therapy with oral anticoagulants might be indicated, whose efficacy is well proven. However it's also linked to a risk of haemorrhage that cannot be neglected. Considering that thrombus formation is mainly linked to left atrial appendage, other non-pharmacological alternatives are being developed, as local therapies. However, evidence and experience about these approaches are lacking from patients with concomitant hepatic disease, making the decision on how and when to start therapy very delicate and stressful.

Methodology: we conducted a research using data sources like Medline Ovid (until January 2018) and the Cochrane Central Registry. We presented our results from the selected articles in tables. Then we analysed our information and built an algorithm.

Results: Traditional anticoagulant therapy and NOACs seem to be safe in patients with mild or moderate hepatic impairment, except for rivaroxaban and edoxaban, whose use is not advised for patients with moderate impairment. Nonetheless, patients should undergo regular monitoring of drug levels and hepatic enzymes. The LAAC techniques are several and one proved to be at least non-inferior to warfarin in a large randomized controlled trial.

Conclusions: More studies are required to proof OAC's efficacy and safety in patients with chronic hepatic disease (CHD), in order to build a guideline for clinicians. The left atrial appendage occlusion has revealed promising results but no study was yet conducted in patients with CHD. Anticoagulant therapy remains the first line for thromboprophylaxis, being LAAC reserved for patients with declared contraindications to OAC.

Keywords: Atrial Fibrillation control, Chronic Hepatic Disease, Stroke/TIA Prevention, Bleeding complications, Therapy.

Resumo **(portuguese language)**

Prevenção do AVC em pacientes com fibrilhação auricular e doença hepática crónica – Revisão

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Introdução: A fibrilhação auricular é uma arritmia frequente e uma causa major de AVC isquémico. O risco de AVC é avaliado através de scores como $CHADS_2$ ou $CHA_2DS_2VAS_c$, podendo indicar o inicio de terapêutica trombo-profilática. A profilaxia do AVC com anticoagulantes orais tem uma eficácia conhecida, porém associada a um risco de hemorragia que não deve ser ignorado. Considerando que a formação de trombos está maioritariamente associada à aurícula esquerda, outras técnicas não farmacológicas estão a ser desenvolvidas de forma local. No caso do paciente também sofrer de doença hepática crónica, a eficácia e a segurança destas abordagens não está ainda esclarecida, sendo a escolha de como e quando começar terapêutica ainda difícil, considerando a pouca evidencia disponível.

Métodos: Realizámos uma pesquisa em bases de dados como Medline Ovid (até janeiro de 2018) e a Cochrane Central Registry. Dos artigos selecionados apresentámos os nossos resultados em tabelas e analisámos o seu conteúdo. Finalmente elaborámos um algoritmo.

Resultados: A terapêutica anticoagulante oral tradicional e os novos anticoagulantes orais parecem ser seguros para doentes com doença hepática ligeira e moderada, exceto o rivaroxaban e o edoxaban, cujo uso não está indicado em casos de doença moderada; os doentes devem sujeitar-se a controlos regulares dos níveis dos fármacos e das enzimas hepáticas. As técnicas de encerramento da aurícula esquerda são diversas e uma delas provou, num ensaio controlado e randomizado, ser não inferior à varfarina.

Conclusões: Mais estudos devem ser realizados a fim de provar a eficácia e a segurança do uso de anticoagulantes em pacientes com doença hepática crónica com o fim de obter uma norma orientadora para a clínica. A oclusão da aurícula esquerda tem-se revelado promissora, porém nenhum estudo foi realizado especificamente em pacientes com cirrose, permanecendo a terapêutica anticoagulante como primeira linha. A alternativa local fica reservada aos doentes cuja anticoagulação está contraindicada.

Palavras-chave: Fibrilhação Auricular, Doença Hepática Crónica, prevenção de AVC/TIA, Complicações hemorrágicas, Terapêutica.

Index

1 | Introduction

Atrial fibrillation (AF) is a frequent cardiac arrhythmia, affecting 0.1 % of adults with less than 55 years and 9.0% of persons aged 80 years or older[1], representing non-valvular AF alone, a five-fold increase in stroke risk[2]. In this condition, the atria activate in a chaotic pattern, leading to an ineffective atrial contraction, propelling thrombus formation and representing a risk factor for thromboembolic events such as stroke. This risk can be assed using the different scales or scores developed by clinicians ($CHADS_2$, ATRIA, $HEMORR_2HAGES$…), and the scores $CHA_2DS_2VAS_c$ (more sensitive to low-risk patients stratification than the older CHA2DS2[2]) and HAS-BLED reunite the biggest consensus among clinicians and investigators[3]. In both cases a high score corresponds to a greater risk of ischaemia or bleeding, respectively, and vice-versa.

The scores take into account multiple risk factors from the patient's profile. The $CHA_2DS_2VAS_c$ score (heart failure, hypertension, age 65-74, age ≥ 75, diabetes mellitus, stroke or transient ischemic attack, vascular disease, female sex) is used to stratify stroke risk in patients with non-valvular atrial fibrillation into risk categories, identifying the patients who would benefit from prophylactic treatment or not. According to the latest guidelines from AHA 2014 should be initiated when the score is more than 2 and for the ESC 2016 when the score is more than 1 in men and more than 2 in woman[3, 4]. In the other and, the HAS-BLED score (hypertension, renal disease, liver disease, stroke or transient ischaemic attack, prior major bleeding or predisposition to bleeding, labile INR, age > 65, medication predisposing to bleeding, alcohol use), also recommended in the most recent guidelines, is important to access the risk of major bleeding events in patients with AF taking oral anticoagulants. This global categorization is helpful for shaping the patient's monitoring scheme, especially in high risk cases, where more frequent patient-doctor visits should be encouraged.

The incidence of AF is higher in patients with non-alcoholic fatty liver disease (NAFLD), the most frequent chronic liver disease worldwide, with up to 40% of NAFLD cases progressing to fatty liver cirrhosis in 10 years[5]. Also, atrial fibrillation and liver disease might share pathophysiological paths, as described by Ya-Hui Ding and his team[6]. Chronic liver disease (CLD) has long been an important obstacle to the use of oral anticoagulants, even now that its applicability and benefits are well described[7, 8]. The reason is most probably related to the bleeding risk associated to oral anticoagulant (OAC) therapy, and to the fear of using it in a group of patients who are considered to be already at a bigger

risk for haemorrhage than the general population. This idea might have limited the inclusion of these patients in some studies about OAC's efficacy and safety.

Indeed, coagulopathy represents a challenge in the follow-up of these patients. The liver is the one responsible for the production of pro-coagulant and anti-coagulant factors involved in the haemostatic system and when the liver is damaged, the parenchyma suffers a reduction in the number of hepatocytes and the liver blood flow is also decreased. Eventually, the synthesis of factors involved in the coagulation cascade and the hepatic metabolism are altered, with decreased levels of the factors II, V, VII, IX, X, XI and also on the levels of protein C, protein S or plasminogen[9, 10], along with a decreased production of platelets with an altered function. Contrarily to earlier beliefs, both haemorrhagic and thrombotic complications might emerge, which motivated clinicians to speak about a new rebalanced haemostasis, where a more fragile equilibrium is obtained[11–13]. Tripodi A. et al studied the role of platelets in the generation of thrombin and they proved that cirrhosis does not affect platelets pro-coagulant activity but if they are in low concentration ($<60x10^9$/L) the production of thrombin may be diminished, correlating thrombocytopenia, frequently found in CHD, with bleeding tendencies.

Further, haemorrhage is currently analysed as an independent risk factor in the decision making process on who, when and how to start anticoagulant treatment. For the bleeding risk assessment, HAS-BLED is the most commonly used score, which predicts bleeding events associated to oral anticoagulant therapy and includes liver disease has a risk factor. A score of ≥ 3 indicates 'high risk' of bleeding [3].

Along with the already described manifestations of chronic hepatic disease there's also oedema, ascites, oesophageal varices, hepatic encephalopathy and, in the case of advanced cirrhosis, the hepatorenal syndrome, lined with altered renal function, demanding frequent dosage monitoring and adjustments when using drugs with renal excretion. Several studies were conducted on this subject, in order to understand the effect of renal dysfunction on oral anticoagulant's metabolism[14, 15] but almost none pondered about the effect of hepatic impairment on the pharmacodynamics and pharmacokinetics of OACs.

Mechanisms related to the hepatic impairment and the drugs own pharmacological characteristics are responsible for the changes in their effects, and emergent data is needed to well document and predict these drugs behaviour under these circumstances. To access the level of hepatic impairment, the Child-Turcotte-Pugh (CTP) score is the most widely used system (Combines the symptoms ascites and encephalopathy with 2 laboratory

parameters, serum albumin, serum bilirubin and prothrombin time), and the MELD score (Model of end-stage Liver Disease) is a simple tool that helps to predict the patient's prognosis. Both of them offer no help on eventual dose adjustments of OAC therapy according to liver function, because they lack the sensitivity to quantify the specific ability of the liver to metabolise individual drugs or predict pharmacodynamics effects.

Even thought there are still no current guidelines on how to manage thrombotic complications in patients suffering from chronic hepatic disease, it has been well established that anticoagulant treatment should not be withheld from patients with cirrhosis even if their profile represents a higher bleeding risk when combined with OAC therapy[4].

The relevance of this subject is obvious as the prevalence of AF is presumed to increase in the coming years[16][17] supporting an eventual increase in the incidence of stroke, making it's prevention a major priority. Another important consideration is that its sequelae also tend to be worse when derived from atrial fibrillation compared to other ethyologies[18].

In AF patients, thromboprophylaxis has been demonstrated to be non-inferior or superior when performed with NOACs in comparison to vitamin k antagonists (VKA) with lower rates of haemorrhagic stroke or other bleeding complications[19–22]. Also, NOAC present many desirable features such as low food and drug interactions, quick onset of action and no need for regular monitoring. Despite the known advantages of the direct oral anticoagulants, experience is still lacking in some "special" groups.

Interestingly, there are other non-pharmacological approaches already approved in the most recent guidelines for stroke prevention in a selective group of patients with atrial fibrillation[3, 4], where left atrial appendage closure (LAAC) assumes an important role and received a class IIb recommendation in patients unsuitable for OAC therapy. These approaches are presently receiving a special attention from the scientific community for its possibilities in patients for whom the use of pharmacological therapies for a long-term of time is considered contraindicated.

Unfortunately, most of the randomized controlled trials that compared some of the different alternatives, excluded patients with hepatic impairment and a direct comparison between the different methods is still non-existent, leaving physicians with no guidelines available to support their work when managing treatment or prevention of thrombotic events in patients suffering from both atrial fibrillation and chronic hepatic disease.

Objectives

The aim of this study was to collect and present data about the safety and efficacy of the different approaches available to prevent stroke in patients suffering from both atrial fibrillation and chronic hepatic disease. We only discussed therapeutic options that are accessible for clinical use.

2 | Materials and methods

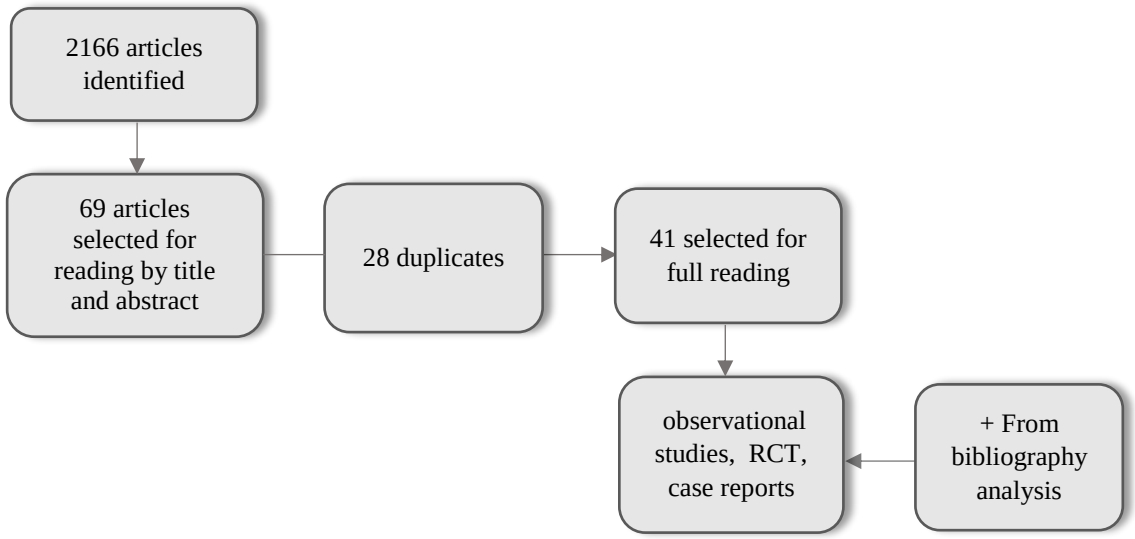

Figure 1 – methodology algorithm

Information sources

Between September 2017 and April 2018, we conducted a research in Medline Ovid and umtil January 2018 in the Cochrane Central Register, using the following terms: atrial fibrillation, chronic hepatic disease, stroke, warfarin, noac, rivaroxaban, apixaban, edoxaban, dabigatran, left atrial appendage, bleeding. We conducted then a selection of the elegible studies and did a further scan to the articles we read fully, collecting others in their bibliography.

Study selection and eligibility criteria

In total, 2166 records were identified from the specified databases. The two investigators independently screened all titles and abstracts. We selected 41 articles for full reading and examination, plus the articles collected from the bibliography, and then we created a table of contents and further analysed if they met the criteria to be included in this review. Our inclusion criteria were as follows: studies of patients with atrial fibrillation in whom the prevention of stroke is being analysed; the patients have contraindications to anticoagulant therapy or suffer from chronic hepatic disease; the studies mention the use of novel oral anticoagulants, warfarin or left atrial appendage.

Given the relatively few studies in populations with chronic hepatic disease, we decided to analyse not only control trials, but also cohorts and registries in populations with contraindications to oral anticoagulant therapy. We excluded trials if they didn't met the eligibility criteria or had no outcomes of interest.

Any disagreements between the two reviewers regarding the eligibility or relevance of specific articles were discussed between them.

We resumed in tables the collected information about the different approaches available and analysed it considering the primary efficacy and safety outcomes. Finally we present our conclusions and propose an algorithm.

3 | Collected data and Clinical Evidence

Oral anticoagulants for stroke prevention in patients with CHD

The efficacy of anticoagulation in reducing the risk of systemic embolization in patients with AF is well established, with an estimated risk reduction in ischaemic stroke events of around 64% - an absolute annual risk reduction of 2.7% in all strokes[31]. For years, warfarin was the most commonly applied therapy for this purpose, with convenient advantages like oral administration and low price.

Effect of hepatic impairment on the Novel Oral Anticoagulants			
in vitro studies			
STUDY NAME	POPULATION	INTERVENTION	RESULTS
Potze W, Arshad F. et al.[9]	Patients with CTP A (n=10), CTP B (n=10), CTP C (n=10) and controls (n=30)	Added 25 ng/mL of rivaroxaban to plasma samples	Dabigatran caused a more pronounced reduction in thrombin generation in patients vs. controls (72.6% in patients vs. 12.8% in controls, P<0.01).
		Added 300ng/ml of dabigatran to plasma samples	Rivaroxaban caused a less pronounced decrease in thrombin generation in patients vs. controls (39.3% in patients vs. 54.5% in controls P<0.01)
Potze W, Adelmeijer J. et al.[32]	Patients with CTP B (n=9), CTP C (n=5) and 11 healthy individuals	Added 25 ng/mL of apixaban to plasma samples	Apixaban lead to a lower decrease in thrombin generation in patients vs. controls (32% in patients vs. 51% in controls, P<0.0001)
		Added 50 ng/mL of rivaroxaban to plasma samples	Rivaroxaban caused a lower decrease in thrombin generation in patients vs. controls (30% in patients vs. 55% in controls, P<0.0001)
In vivo studies			
STUDY NAME	POPULATION	INTERVENTION	RESULTS
Kubitza et al.[33]	Patients with CTP A (n=8), CTP B (n=9) and matched healthy controls	single oral dose of 10 mg of rivaroxaban after 10h fasting period	- Subjects with mild hepatic impairment had similar inhibition of Factor Xa activity vs. controls, and similar PT prolongation. - Subjects with moderate hepatic impairment experienced an increased and more sustained inhibition of Factor Xa activity (28% after 24 h in subjects with moderate hepatic impairment vs. 4% in healthy subjects), and PT prolongation was more pronounced in subjects with moderate hepatic impairment (2.14-fold).
Stangier et al.[34]	Patients with CTP B (n=12) and matched healthy controls	single oral dose of 150 mg of dabigatran etexilate	- Mean half-life (11.5 controls vs. 11.8 in patients) and clearance period (65.2mL/min in controls vs. 63.1mL/min in patients) of dabigatran were similar between groups. - Median tmax of dabigatran was achieved 2 hours after drug administration in both groups. - Ratios of the area under the concentration-time curve (AUC) and Cmax in controls vs. patients showed an average 5.6% decrease of AUC (94.4; 90% CI, 52.2-171) and 30% (70.2%; 90% CI, 38.5%-128%); Cmax was lower in patients with hepatic impairment (76.1 ng/mL vs with 107 ng/mL in controls);

			- Baseline PT time was prolonged in patients with hepatic impairment vs. controls (INR was 1.40 in patients vs. 1.02 in controls). Baseline activated partial thromboplastin clotting time (aPTT), ecarin clotting time (ECT), thrombin time (TT) were unchanged.
Frost et al.[35]	Patients with CTP A (n=8) or B (n=8) and matched healthy controls	single oral dose of 5 mg of apixaban + lidocaine 1mg/kg 4 days later	- Area under the concentration-time curve point estimates and 90%CI were 1.03 (0.798, 1.32) for mild impairment and 1.09 (0.849, 1.41) for moderate hepatic impairment vs. controls. - Protein binding was 93%, 93% and 92% for controls, mild impairment and moderate impairment groups, respectively. - Baseline INR was higher in patients vs. controls, but percentage changes from baseline were similar across groups.
Mendell et al.[36]	Patients with CTP A (n=8), CTP B (n=9) and matched healthy controls	single 15mg dose of edoxaban to every patient	- Mean baseline PT values were elevated in subjects with mild (12.3 seconds) or moderate (13.3 seconds) hepatic impairment compared with their respective controls (11.3 and 11.0 seconds). - Cmax of edoxaban was similar between subjects with mild impairment vs. controls; but the median tmax was 2 times higher for the moderate hepatic impairment cohort vs. controls. - $t_{1/2}$ of edoxaban was longer for subjects with hepatic impairment, (1 hour increase for mild and 1.4 hours for moderate) vs. controls. - Subjects with mild or moderate hepatic impairment had slightly lower total exposure to edoxaban vs. controls.

Table 1 – The effect of hepatic impairment on NOACs *in vitro* and *in vivo.*

In a real life context, even after AF is diagnosed and the risk for stroke is identified, only a percentage of patients receives anticoagulant treatment and only 50% keeps taking it after 3 years of initiating treatment[37, 38]. Moreover, the patients often have an INR outside of the therapeutic range, and the need for regular monitoring and frequent dose adjustments end up being the biggest disadvantages of VKAs in what concerns the patient's adherence to therapy. To note that the efficacy and safety of VKAs are dependent on the quality of their management, where an INR below the reference represents a risk for thrombosis and an INR above increases the risk of bleeding[39]. This interpretation is very difficult in patients with cirrhosis due to it's impact on coagulation and clotting system. In spite of that, the biggest influencer in therapy dropouts are bleeding tendencies, the main side effect of OAC therapy.

Until 2008, Vitamin K antagonists were the only drugs approved for stroke prophylaxis, when the novel oral anticoagulants emerged and brought new possibilities to the clinicians. NOACs have a more predictable pharmacokinetic profile, exhibiting their effect by directly inhibiting a single factor in the coagulation cascade. They're administered at fixed doses and

dispense routine monitoring. Also, they may have less interactions with food and drugs compared to VKAs[40]. Several studies, randomised trials and indirect comparisons, were then conducted to prove NOACs efficacy and safety, and all of them showed to be non-inferior or even superior in terms of efficacy for stroke prevention and presented lower rates of intracranial bleeding with respect to warfarin[19–22, 41]. But none actually compares NOACs against each other, excluding, the majority of them, patients with hepatic impairment.

STUDY NAME	POPULATION	INTERVENTION	CONTROL	End Points	
				Efficacy	Safety
Seung-Jun Lee et al	321 patients with cirrhosis and AF (mean CHA_2DS_2-VASc VKA group 2.6 ± 1.8; no VKA goup 2.2 ± 1.5)	VKA (CTP A n=108 + CTP B or C n=65)	No VKA (CTP A n=107, CTP B or C n= 41)	VKA 1.8% No VKA 4.7%	VKA: CTPA 5.62%, CTP B or C 18.03% (mean 9.61); No VKA: CTP A 5.20%, CTP B or C 9.15%
Efficacy end point: Ischaemic stroke events Safety end point: Major bleeding events					

Table 2 – Comparing the impact of VKA in stroke and bleeding risk in patients with hepatic impairment

Seung-Jun Lee[28] and his team published a cohort analysis with 321 patients with atrial fibrillation and chronic hepatic disease (CTP A n= 215, CTP B or C n= 106) and concluded VKA therapy reduced the risk in early stage liver cirrhosis patients without increasing the risk of major bleeding. But, in patients with advanced liver cirrhosis, the difference in stroke risk was not significant and the risk of major bleeding events increased (Table 2). These results reveal the importance of liver disease severity as a risk factor when choosing to implement VKA.

As described before, hepatic impairment can alter the anticoagulants' effect, among other reasons, due to coagulopathy, to altered metabolisation of drugs and for altered bioavailability, a consequence of the decreased levels of albumin, affecting essentially molecules with high binding properties [43]. Since anticoagulants undergo hepatobiliary metabolism, they should be used with caution, with regular follow-up and frequent laboratory monitoring, until more data are available on their safety in patients with liver dysfunction.

In relation to esophageal varices, they contribute to increment the risk of gastrointestinal bleeding, whose presence in patients taking anticoagulant therapy can be considered

dangerous[28], which motivated their exclusion from trials evaluating NOACs in AF patients. A study evaluated the use of traditional anticoagulants in 136 patients with portal hypertension and esophageal varices and from them 84 received anticoagulant therapy. No relation was found between the use of OAC and bleeding risk, if there was being applied treatment to manage varices[29], which could be with the use of non-selective b-blockers or endoscopic ligation[30], and also avoidance of anti-inflammatory drugs and estrogens. It was concluded that it was the varices size that played a major role on bleeding risk. Condat et al. actually propose that the prevention of thrombosis in the venous system and its effect in not raising portal pressure may be an important key player in bleeding risk reduction[29]. To note that these findings weren't validated in NOACs.

Instead of large prospective trials, some of the available data on the effect of hepatic impairment on oral anticoagulants and their safety and efficacy on stroke prophylaxis are from small clinical retrospective trials and *in vitro* studies, which have limited relevance. It has been proposed from an *in vitro* trial, with a thrombin generation assay being used to assess anticoagulation potency, that the direct inhibitor of thrombin, Dabigatran, has increased anticoagulant effect in patients with severe hepatic impairment[9]. The reduction in thrombin generation reflects the level of liver disease. These data suggest that dabigatran, in standard dosing regimens, may lead to higher than desired anticoagulant effect in all types of cirrhosis patients. This finding, however, has not been established in clinical studies, *in vivo*. In a protocol[34] with a single dose administration of Dabigatran in healthy controls vs patients with CTP B (n=12) no differences were observed in coagulation markers or drug exposure[34], between groups. One of the described secondary effects of dabigatran is dyspepsia, probably due to the tartaric acid present in the dabigatran etexilate capsules[44], but it's use with a proton-pump inhibitor compromises it's absorption and efficacy. Also, if we consider the findings from the RELY trial[22], it were described higher rates of gastrointestinal bleeding comparing to warfarin, raising a question when it comes to patients with chronic liver disease and oesophageal varices, a topic requiring further attention. Finally, simultaneous administration with P-glycoprotein inhibitors and inducers should be carefully analysed, because dabigatran is a P-glycoprotein substrate[14].

Rivaroxaban is a factor Xa inhibitor, metabolized via the CYP450 system, and a substrate of P-glycoprotein[14]. It is administered in a single daily dose, which could help to improve patient's compliance. In rivaroxaban's *in vitro* testing[9, 32], the effect of anticoagulation was showed to be decreased in patients with severe hepatic impairment (CTP

C), and no difference was described between patients with CTP A or B versus controls. Kubitza et al.[33] tested the effect of a single 10mg dose of rivaroxaban in patients with mild (n=8, CTP A) and moderate (n=8, CTP B) hepatic impairment, observing a moderate increase in the levels of drug exposure and prolongation of PT in patients with moderate hepatic impairment; the clearance was reduced and also the levels of FXa activity. Maybe for this reason, the use of rivaroxaban is not recommended in patients with CTP B or C (not included in the study) cirrhosis or in any patient with hepatic disease associated with a coagulopathy. The patients with mild hepatic impairment had minimal impact and no major adverse events occurred during the trial. The first and largest clinical study comparing the use of NOAC (n=20) in cirrhosis patients with a comparison cohort of patients taking traditional anticoagulants (n=19) is from Intagliata M. et al and lasted for 3 years. There were 6 patients with atrial fibrillation and the study concluded that the rate of total documented bleeding events was similar between the two groups (4 in the NOAC group and 3 in the traditional therapy group) and also the rate of major bleeding (1 in the NOAC group – patient on rivaroxaban – and 2 in the traditional therapy group)[45]. Patients with CTP C were excluded.

Apixaban, also an inhibitor of factor Xa, has the highest percentage of hepatobiliary metabolism of all NOACs, requiring more caution in the setting of advanced hepatic failure. Careful monitoring of drug levels can be accessed by anti-Xa testing[27]. Apixaban is also metabolized via the CYP450 system, leading to certain drug interactions and, like the other factor Xa inhibitors, apixaban is a substrate of P-glycoprotein. The *in vitro* observation showed a decrease in anticoagulant potency in patients with moderate or advanced cirrhosis – CTP B or CTP C [32]. C.E. Frost et al. tested the effect of a single 5mg dose of apixaban in patients with mild or moderate hepatic impairment, and no relevant changes were observed between groups[35] suggesting apixaban has a predictable profile and no dose adjustments are required in patients with mild or moderate hepatic impairment. In the already mentioned clinical trial, from Intagliata et al. 9 patients received apixaban and the anticoagulant effect remained practically unchanged in patients with CTP A or CTP B, compared to patients receiving traditional anticoagulation[45].

Edoxaban is the most recent factor Xa inhibitor and is applied once daily. It is metabolized via hydrolysis and it's free from interactions with the CYP450 system, but interactions with P-glycoprotein (P-gp) inhibitors exist, which motivated an indication to reduce dosage to half when there is concomitant use of verapamil, an antiarrhythmic agent

and potent P-glycoprotein inhibitor[26]. A study examining the effect of a single dose 15mg of edoxaban in patients with CTP A (n=8) and B (n=8) found no difference in drug exposure between groups and the pharmacokinetics and pharmacodynamics were similar compared to healthy subjects[36]. Again, knowledge of drug metabolism and effects in patients with hepatic impairment is very limited.

STUDY NAME	POPULATION	INTERVENTION	CONTROL	**End Points**	
				Efficacy	Safety
Justine Hum et al	45 Patients with cirrhosis, 24 with AF	Rrivaroxaban 20mg daily (n=17) Apixaban 5mg twice a day (n=10)	Warfarin (n=15) Enoxaparin (n=3)	Rivaroxaban or Apixaban 0% VKA or LMWH 0%	Rivaroxaban or Apixaban 1% VKA or LMWH 5%
N. M. Intagliata et al	39 patients with cirrhosis (CTP A n=18, CTP B n=21), 5 with AF	Rivaroxaban 20mg daily (n=9) Apixaban twice a day (n=11)	Warfarin (n=13) Enoxaparin (n=6)	Not mentioned	Rivaroxaban or Apixaban 5% VKA or LMWH 11%
Efficacy end point: Ischaemic stroke events Safety end point: Major bleeding events					

Table 3 – Results from studies comparing the use of traditional anticoagulation and NOACs.

A retrospective cohort[46] from a sample of 45 patients with mild or moderate hepatic impairment (CTP class A and B), in which 24 had atrial fibrillation, evaluated safety and efficacy of traditional OAC therapy (warfarin n=15, LMWH n= 3) versus NOACs (rivaroxaban n=17, apixaban n= 10) during a period of 3years. 18 Patients received traditional therapy (9 had AF) and 27 received a NOAC (15 had AF). 10 patients had a bleeding event on traditional therapy and 8 on NOACs. From the traditional therapy group, 5 where major bleeding and 3 where intracranial bleedings and 1 major bleeding was associated with NOAC with no intracranial bleeding described. These results may suggest NOACs have a safer profile. During follow-up there were no ischaemic strokes. From this study is missing the information on average $CHA_2DS_2VAS_c$ score and HAS-BLED.

Considering drug interactions with the oral anticoagulants, the VKAs have the biggest number of cases, but NOACs have some interactions too. Like mentioned above, they are substrates of the p-glycoprotein transport system (P-gp), meaning their plasma concentration will be affected by both inhibitors and inducers of P-gp. There are several drugs which are substrates of the P-gp pathway (eg. verapamil, amiodarone), that are commonly used in AF patients, requiring caution when administering them concomitantly[47]. Other interactions are

related to cytochrome P540 3A4 (eg. calcium channel blockers), one of the metabolisation pathways of rivaroxaban and apixaban.

ORAL ANTICOAGULANTS IN ATRIAL FIBRILLATION					
	Warfarin	**Dabigatran**	**Rivaroxaban**	**Apixaban**	**Edoxaban**
Mechanism of action	Vitamin K antagonist	Inhibits factor IIa	Inhibits factor Xa	Inhibits factor Xa	Inhibits factor Xa
t 1/2	24-58h	12-17h	5-9h	12h	10-14h
Elimination	92% renal, 8% gastro-intestinal	80% kidneys; 20% gastro-intestinal	66% kidneys ; 34% gastro-intestinal	27% kidneys ; 73% gastro-intestinal	50% kidneys; 50% gastro-intestinal
Onset of action	3 – 5 d	2h	2 – 4 h	3 h	1 – 2 h
Regular dose	According to INR	75 or 150 mg 2x/d	10 or 20 mg /d	2,5 or 5 mg 2x/d	15 or 30 or 60 mg /d
Indications	VTE; Stroke; EAM	VTE; Stroke	VTE; Stroke	VTE; Stroke	VTE; Stroke
Antidote	Vitamin K PCC	Idarucizumab	Adexanet alfa	Adexanet alfa	Adexanet alfa
Effect of hepatic impairment	*adjustments according to INR	Safe in CTP A/B without adjustments. Attention when liver enzimes are altered.	Apparently safe for CTP A. Contraindicated for CTP B/C	Safe in CTP A, without adjustments. Apparently safe for CTP B/C. Attention when liver enzimes are altered	Safe in CTP A without adjustments. Not recommended in CTP B/C
Drug interactions	Numerous drugs involving substrates of CYP2C9, CYP3A4, and CYP1A2	Strong P-gp inducers or inhibitors	Strong CYP3A4 inducers; Strong inhibitors of both CYP3A4 and P-gp	Strong inducers or inhibitors of both CYP3A4 and P-gp	Strong P-gp inhibitors
Drug monitoring	INR	Modified thrombin time test	anti-FXa assay	anti-FXa assay	anti-FXa assay
PCC: Factor IV prothrombin complex concentrate					

Table 4 - Resume of oral anticoagulants' characteristics [9, 32–36, 40, 42, 48, 49]

Reviewing, the current guidelines and approval information[50–53] do not recommend the use of any of the anticoagulants in patients with severe hepatic impairment (CTP C) and in those with associated coagulopathy and clinically relevant bleeding risk. In warfarin's case, it's use is recommended with caution and according to the INR value. For the NOAC, no restrictions are imposed on their use in patients with mild hepatic disease (CTP A). According to the approved prescribing information, apixaban requires no dose adjustments in patients with CTP A cirrhosis, but no specific recommendations exist for patients with CTP B. However, the use of apixaban must always be prudent because it has higher hepatic metabolism than the rest of the NOACs and it's use is not recommended if the levels of the

hepatic enzymes, AST and ALT, are twice the upper limit of normal or in patients with CTP C cirrhosis. Dabigatran too is not recommended in patients with elevated liver enzymes and it's use is apparently safe in patients with moderate hepatic impairment. Rivaroxaban is not recommended in patients with moderate or severe hepatic impairment (CTP B and CTP C) or in any degree if associated with coagulopathy; no dosage recommendations are established for patients with CTP A cirrhosis. Edoxaban, similarly is not recommended in patients with moderate or severe hepatic impairment (CTP B and CTP C). Further, according to the ESC 2016 guidelines, warfarin receives a level IA recommendation and dabigatran, rivaroxaban and apixaban a level IB, these ones recommend for patients with difficulties to maintain a therapeutic INR with warfarin.

Overall, no dose adaptations are recommended for any of the mentioned agents when used in patients with CHD, reflecting the insufficient data and the limited clinical experience in these patients. The only studies concerning the effect of NOACs in patients with chronic hepatic disease were performed *in vitro* or on a single dose basis.

Reversal agents for the Oral anticoagulants

For many physicians, the lack of an agent to reverse the novel oral anticoagulants effect may cause discomfort when deciding to administrate them. Even though safety studies in NOAcs are reassuring, the management of a serious bleeding event remains a challenge. While physicians have a vast experience with warfarin's use, there is still big concern about NOACs and the lack of widely available antidotes. The prothrombin complex concentrates (PCC) and activated PCC, recombinant factor VII were being used as reversal agents before new agents came along[54]. Recently the FDA and the EU approved the use of Idarucizumab, an antibody fragment that binds to dabigatran with an affinity 350 times higher than observed with thrombin, which proved to have a rapid and complete reverse response[55] even under urgent circumstances. Adexanet alfa was also approved by the FDA[56], very recently on May 2018, and Ciparatang another more "universal" reversal agent, is still under study but it's also presenting enthusiastic results[54].

Left atrial appendage ligation and closure

Study name	Device	Follow-up	mean CHA_2DS_2VASC	mean HAS-BLED	Implant success (%)	Peri procedure events (%)	Stroke % per year	Major bleeding % per year	PPT
Boersma et al.[57]	Watchman	1 year	4.5	2.3	98.5	2.8	1.1	2.6	Dual or single antiplatelet therapy for 6 months and OAC
Reddy et al.[58]	Watchman	1.2 year	4.4	NR	94.7	8.7	2.3	NR	Dual antiplatelet therapy 6 months and lifelong aspirin
Tzikas et al.[59]	Amplatzer	13 months	4.5	3.1	97.3	4.9	2.3	2.1	Single or double antiplatelet therapy 1-3 months followed by single antiplatelet therapy other 3 months minimum.
Urena et al.[60]	Amplatzer	20 ± 5 months	5	4	98.1	5.8	1.1	1.9	Single or double antiplatelet therapy for 1-3 months, followed by single antiplatelet therapy
Kebernik et al.[61]	Amplatzer	9 months	5	3	100	7.3	2.2	1.1	Dual antiplatelet therapy for 6 months and lifelong single antiplatelet therapy
Minguez et al.[62]	Amplatzer	2 years	4	3	94.6	5.4	2.4	3.1	Clopidogrel 3-6 months and aspirin until 6-12 months
Berti et al.[63]	Amplatzer	30 months	4.3	3.4	100	3.6	2.2	1.1	3 months dual antiplatelet therapy followed by single therapy
Seeger et al.[64]	Amplatzer Watchman	1.1 years	4.4	4.2	NR	3	2%	NR	3-6 months dual antiplatelet therapy followed by long-term therapy with aspirin.
Price et al.[65]	Lariat	112 days	4.1	3.2	94%	9.7%	1.3	NR	Single or double antiplatelet therapy (55%) or no therapy (19%)
Lakkireddy et al[66]	Lariat	1 month	3.9	3.4	98%	10.1 to 2.2*	NR	NR	Single antiplatelet therapy

PPT: post-procedure therapy more frequently applied
NR: not reported
*rate changed according to the needle used during procedure

Table 5 – Implantation devices and study results from populations with contraindications to OAC

In patients with non-valvular AF, thrombus formation his mostly taking place at the left atrial appendage (LAA)[64], partly related to its morphology[67]. Considering the limitations described to OACs use, alternative methods were studied and developed as local therapies. The left atrial appendage occlusion and excision or ligation are promising alternatives, available for patients with contraindication to OAC therapy, providing the desired cardioembolic protection and removing the need for long-term OAC therapy. The 2016

European guidelines and the 2014 American Heart Association/American Stroke Association guidelines for Stroke and TIA gave a class IIb recommendation, level of evidence B for percutaneous LAAC in patients unsuitable for OAC[4].

There are different techniques presently accessible in clinical practice. Surgical left atrial appendage closure is being performed since 1940 and is still currently used during cardiac surgery, for other motives than atrial fibrillation, by suture, staples or clips[68]. The LAA ligation, however, might be incomplete and these patients will continue at risk for thrombus formation, if not at a greater risk[69]. Also, not all thromboembolic events derive from the LAA and there's still at risk of thromboembolic events derived from the aorta and from carotid atherosclerosis[48].

Besides that technique, other new and less invasive options exist nowadays. They are non-surgical, minimally invasive catheter-based interventions that consist in the introduction of a device and it's placement at the LAA. PLATOO was the first system designed to perform endocardial LAA occlusion on the market and, although it showed promising results, even in patients not eligible for anticoagulant therapy[70, 71] [72], it was removed from the market in 2006.

The WATCHMAN device came next. It started being implanted in 2002, and consists of a permanent self-expandable implant, permeable to blood and, for this reason, its manufacturer recommends the use of thromboprophylatic drugs until endothelialisation is complete. Therefore, during the periprocedure period and for a variable period after, the risk of bleeding events will be increased. The absence of residual flow in the LAA defines the success of the implantation. Several studies were conducted on the safety and efficacy of this approach. The PROTECT AF [73] study was a non-inferiority randomised control trial (RCT), involving 707 patients with non-valvular atrial fibrillation, randomly assigned to device implantation and temporary post-implant OAC therapy and lifelong aspirin, or to long-term warfarin therapy, in a 2:1 ratio (463 / 244). The 3.8 years follow-up analysis, proved this technique was not only non-inferior to warfarin but also superior, when considering combined outcomes of all strokes, systemic embolism, cardiovascular death and all-cause mortality[74]. Later, the PREVAIL trial revealed an improvement on procedural safety but the non-inferiority criteria were not achieved. The major complications related to this approach are described, and consist mostly of pericardial effusion, with tamponade, procedure air embolism and acute stroke and the events rate seems to be related to the

operator experience, decreasing when this increases[73]. In both of these RCT, the patient's inclusion criteria did not included subjects with hepatic impairment. Still and all, we consider that describing the data available on these approaches in populations with contraindications to anticoagulant therapies can be revealing, allowing to make some previsions for the cases where chronic hepatic disease is an issue.

More recently, the Ewolution[57, 75] registry included 1021 patients at high risk of stroke and moderate-to-high risk of bleeding, which they considered to be representative of a real-world population. From them, 73% of patients were unsuitable for OAC therapy (the criteria are not described) and 4.3% had hepatic impairment. After implantation, anticoagulants were recommended for 3-6 months, so that 27% stayed with OAC, 59% with dual anti-platelet therapy, 8% on single antiplatelet therapy and only 6% without any type of OAC. In this study, 98.5% of the patients were successfully implanted (absent or minimum residual flow in 99.7%). Importantly, the incidence of periprocedure complications did not differ between subjects on OAC vs. not on OAC therapy after implantation, but was significantly lower in patients previously considered ineligible for OAC compared with eligible patients. Finally, for those with high risk of bleeding (HAS-BLED >3), the events rate was superior. The results from the 2-year follow-up were not released yet, but we can already appreciate that this device has a good sealing success and seems to be safe and effective in stroke risk reduction (At 1 year follow-up, 73% of patients weren't taking any oral anticoagulant and 1.1% had a stroke).

The ASAP trial [58] analysed the safety and the efficacy of LAA closure with the Watchman device in a group of 150 patients who had contraindication to warfarin therapy, mostly related to bleeding tendencies, but who were eligible to antiplatelet therapy; none had chronic hepatic disease. After device implantation, with a success rate of 94.7%, patients received antiplatelet therapy with clopidogrel or ticlopidine for 6 months and lifelong aspirin. The device showed to be safe and effective without the need for warfarin therapy in the post-implant period. The procedure and device related events occurred in 8.7% of the patients and the annual rate of all cause stroke observed was 2.3% (1.7% ischaemic stroke, 0.6% haemorrhagic stroke).

The other device available for LAA closure is the Amplatzer Cardiac Plug, a self-expanding double-disc nitinol frame covered with a polyester patch that was primarily developed for closure of atrial septal defects. A report from 2011 described, retrospectively, the initial European experience[76] on this device during the first 24h, involving 143 patients,

with an implantation success of 96% and a periprocedure complications rate of 7%. This patients were kept on heparin during procedure and continued DAPT for 1-3 months and 5 more months on aspirin alone. Then, a multicentre registry from 22 sites in Europe, including 1053 patients, reported a procedural success rate of 97.3%, an annual rate of systemic embolism of 2.3%, and a complications rate of 4.9%[59]. They verified patients who were under more intense antithrombotic therapy had more major bleeding events, and also that patients taking no therapy rather than aspirin after procedure were at higher risk for ischaemic events (TIA and stroke).

Several registries followed, with smaller populations, like the Iberian registry[62], with the involvement of 167 patients, reporting an implant success of 94.6% and a periprocedure event rate of 5.4%. An Italian single center registry[63] described an implant success of 100% and a complications rate of 3.6% and a Canadian single center registry[60] described a 98.1% success of implantation and a complications rate of 4.9%; patients underwent LAA closure with Amplatzer device and received 1 to 3 months DAPT and then single platelet therapy[60]. Other single center registry from the University of Kiel[61] reported an implantation rate of 100% and a periprocedure events rate of 7.3%. A registry from the Cardiology department of the University of Ulm[64], involving 101 patients with non-valvular AF who were unsuitable to take oral anticoagulant therapy, assigned patients to Watchman (n=38) implant or to the Amplatzer device (n=63), based on morphology of LAA; patients then received double antiplatelet therapy for 3 or 6 months after implant. The results showed no difference between the two devices for the main efficacy outcome (2%) groups or for the fact that patients were prescribed with DAPT for 3 or 6 months. For the bleeding events rate, it was lower with 3 months on DAPT compared to 6 months[64].

Then, another approach started to be carried out more recently, the percutaneous epicardial LAA occlusion and several devices are now under development[48]. Among them, the Lariat suture device, introduced via femoral and with epicardial access via catheter, was already approved in the EU and was tested in a RCT for preclinical data to test its feasibility in humans[77]. Matthew J. Price et al.[65] conducted an investigation about the safety and efficacy of this technique in 154 patients from 8 centres in the US, with the primary end point defined as implantation success, which was achieved in 94% of the cases, and had 10% major procedure complications, the majority from major bleeding events. The average time of follow-up were 112 days, and from the 134 with possible follow-up, 2 had a stroke, causing the death to one of them. The biggest advantage of this technique is that it doesn't

leave any instrument behind, which would require anticoagulation until endothelialisation was complete, and also the fact that size and the morphology of the auriculae don't influence the approach. The major complications of the Lariat technique are cardiac perforation related to the epicardial access and pericardial effusion. A more recent registry[66], with data from 18 centres in the US, involving 721 patients, declared an implant success rate of 98%. Then they realized the periprocedure complications ate was different according to the needle used for pericardial access, varying from 10,1% with the large-bore needle to 2,2% with the micro-puncture one. In both cases, no homogeneous post-procedure protocol was followed, varying from anticoagulated states to double antiplatelet therapy to no agent at all.

The main advantage of the LAAC procedure is making long-term OAC therapy unnecessary, and it should be considered in patients with both high risk of stroke and haemorrhage. These techniques are not recommend in low risk cases because of the complications experienced during the periprocedure period, with higher rates than the thombo-embolic risk, camouflaging the net clinical benefit of these options. Moreover, their efficacy and superiority over oral anticoagulant therapy, in patients with contraindications to OAC, is not entirely established yet. From these studies, only one RCT and two cohorts enrolled patients with known hepatic impairment. EWOLUTION enrolled 1021 patients and 4.2% of them had liver impairment; Urena et al. involved 52 patients and 3,8% had liver disease, Matthew J Price et al. involved 154 patients and 6% had liver impairment.

5 | Discussion

There is a considered amount of patients with atrial fibrillation and at high risk for stroke, who require thromboprophylatic treatment, with a well-established net benefit, but who also present high risk for bleeding, not only derived from oral anticoagulant therapy intake but also from other comorbidities, like chronic hepatic disease. For these patients, the best approach is unclear, raising the question of exactly which patients will benefit from which type of therapy, pharmacological or not.

For a long time, oral anticoagulant therapy has been the gold standard therapy for stroke prophylaxis in patients with AF, and warfarin assumed the main role. With the rise of the new anticoagulants, studies were conducted to establish their safety and efficacy, and all of them proved to be superior compared to warfarin in the primary efficacy outcome[19–22], also a reflex of a reduction on intracranial haemorrhage events. However, these conclusions were established in populations without liver impairment. Withal, the novel oral anticoagulants presented wider gastrointestinal effects than warfarin, except for Apixaban[78], and this observation has an enhanced importance in cirrhotic patients who might present with esophageal varices, a major risk factor for gastrointestinal bleeding.

At the moment, no large, well-powered, prospective trial exists examining the safety of any therapeutic anticoagulant agent in cirrhosis patients, but considering the available information, we can already highlight the importance of "drawing" a personalised treatment for each patient. It's essential to take the patient's risk profile into account, employing variate scores and to access also the level of hepatic impairment and notice if esophageal varices or thrombocytopenia are present.

However, these risk-stratification algorithms derive originally from clinical-trial cohorts with careful patient selection and close monitoring, not necessarily reflecting real-world situations. In fact, many patients at high risk for bleeding were excluded from these studies[23]. They were not build to be used in patients with chronic hepatic disease and the quality of their information might be inaccurate. The HAS-BLED score, unlike the CHA_2DS_2VASc, has a risk criteria for major bleeding in patients with abnormal liver function and with atrial fibrillation under anticoagulant therapy, considering the eventual thrombocytopenia, splenomegaly or prolonged international normalized ratio (INR), which coexist with haemorrhagic diathesis[24].

Another issue is related to the monitoring tests available in clinical practice. The coagulation tests: aPTT (activated partial thromboplastin time) and PT (prothrombin time) are used to estimate the risk of bleeding, and treatment with warfarin is monitored with INR (international normalized ratio), based on PT level. However, these results are poorly correlated with the bleeding tendencies, has they are designed to assess isolated defects of pro-coagulants, but are insensitive for anticoagulant factors[11]. Nowadays the anti-FXa assayis the current recommended procedure to monitor the direct factor Xa inhibitors levels and, for the thrombin inhibitor, the modified thrombin time test is an available option[26, 27].

Additionally, physicians make a subjective evaluation, identifying risk factors outside of the scales and different weights might be attributed to different factors. Also, the intervention in modifiable risk factors can have a major role in prevention of ischaemic and bleeding events (hypertension, management of OAC therapy, co-medication with antiplatelet or NSAID, alcohol intake, etc)[4, 25] and are specially the patients with a "special" risk profile that demand the biggest attention, due to the multiple morbidities and varied medication.

For all these reasons, the different treatment options should be evaluated, presented and discussed to and with the patients, in order to provide the best care according to the patient's expectancies, explaining the possibilities and the limitations of the different approaches available [Figure 1]. This consultation gives the patient a chance to make an informed decision about its treatment, which usually helps with therapy adherence issues.

Interestingly, the benefits associated to OAC therapy in patients affected by both AF and CHD go beyond stroke prophylaxis. They are also recommended for portal vein thrombosis prevention[8, 79] and more interestingly, they proved to play an important role in disease modification in patients with chronic hepatic disease, by blocking fibrogenesis[80] through the inhibition of fibrin and factor Xa, as there is a known link between the activation of the coagulation cascade and the progression of liver fibrosis. Also, atrial fibrillation and liver disease might share pathophysiological paths, which may serve as common therapeutic targets[6], deserving more investigation in the near future.

To be able to build a trustworthy guideline for physicians on the proper use of anticoagulation, more studies are required, pooled long-term analysis, comparing the NOACs among each other and enquiring why each one of the anticoagulants could be superior, in terms of safety and efficacy, and for which patient. Until today, the

pharmacological properties of all anticoagulants in cirrhotic patients are still poorly understood. Concerning the safety and efficacy of traditional therapies in cirrhotic patients, they were established for a group of selected patients, with compensated disease[28]; and in a small comparison between traditional anticoagulants with the two NOACs, rivaroxaban and apixaban, the bleeding risks were shown to be similar[45], or even lower with the novel agents[46]. However, this is not enough to cover all the patients admitted at the hospital. Regarding the NOACS, all we have on our disposal are *in vitro* studies[9, 32], small retrospective trials or registries[45, 46] with considerable variations in study design, describing their characteristics and proposing how hepatic impairment can affect their properties, based on observations after single dose administrations[33, 34, 36].

Until now, no formal dosing adjustments or monitoring advertisements were recommended for cirrhotic patients, and although the most recent guidelines advise the use of NOACs when the patients have difficulty to maintain a stable INR, it's also true that no anticoagulant is recommended in patients with severe hepatic impairment (CTP C), with high risk of bleeding and coagulopathy. Only dabigatran is apparently safe in patients with moderate hepatic impairment[34], and parallel to apixaban, their use must be prudent according to the levels of the liver enzymes. Both rivaroxaban and edoxaban are not recommended for patients with CTP B or CTP C.

For their many characteristics, like easier monitoring and improved rates on haemorrhagic stroke, the novel oral anticoagulants are expected to replace VKA as the first-line medication in stroke prophylaxis, but its safety and superiority is still not proved in patients with chronic hepatic disease.

For the listed reasons, even with the different oral anticoagulant options, there is still a great number of patients that will continue to be poor candidates for long-term anticoagulant treatment. At present, LAA amputation, ligation, or occlusion provide an acceptable solution for some of these patients, which from the presented trials (Table 5) has an implant success non-inferior to 94% with stroke rates per year inferior to 2.4%. The LAAC approach counts with several different devices, some not available in the United States (US) but available in Europe (EU), like the Amplatzer plug and the Lariat system. The Watchman implant is the one with more robust results, approved in EU and by the FDA, in the US, which proved to be at least non-inferior to warfarin, in patients with[57, 58] and without contraindications to OAC. Indeed, long-term trials found that patients experience lower rates of major bleeding events after the periprocedure period, when using this device, than the ones receiving long-

term warfarin[81]. The Watchman device is indicated[4] to reduce the risk of thromboembolism in patients suffering from non-valvular atrial fibrillation with increased risk of stroke, requiring thromboprophylatic therapy (with a $CHADS_2$ equal or more than 2) but who were deemed unsuitable for warfarin, p.e because they have difficulties to follow up closely their INR, or experienced stroke even on anticoagulant regime. Also, they must have a compatible profile to beneficiate from this technique and they must be aware of the implications related to it. Future studies should investigate if a comorbidity of chronic hepatic disease affects patients' outcomes.

Although there is indirect comparative data proposing that LAA occlusion with the Watchman device is non-inferior to DOACs[82] in patients without contraindications to OAC, there have been no prospective randomized controlled trials to compare these two management options, or an OAC with any other device. The PRAGUE-17 study is a randomized controlled trial that will compare percutaneous LAA occlusion with either the Amplatzer Amulet or the Watchman device versus DOACs[83] in patients both at risk for stroke and bleeding, filling this gap partly. But again, these trials are not focused on populations with hepatic impairment.

In consideration to the other percutaneous left atrial appendage closure strategies, it's difficult to establish more conclusions given the amount and the quality of the clinical trials, with a mix of retrospective and prospective data, and lacking randomization. The Amplatzer Amulet device received a CE approval in EU for LAAC, and also showed some impressive results, majoritarily from small registries, and involving patients with contraindications to OAC. The Lariat Loop system is another device approved in EU, also evaluated in small trials, whose difference from the two mentioned systems consists on the implantation technique and purpose, being more indicated for patients without a suitable anatomy for endocardial LAA occlusion. It is placed via epicardial access and it's supposed to close the auricula from the inside[65]. Because it's not a real implant and doesn't require endothelisation, like the Watchman implant p.e., it might be an interesting solution to offer to patients unsuitable to anticoagulants, whose use in this case might be unnecessary. Also to point out that the the study from Lakkireddy et al. revealed how a small change in the protocol can improve outcome results, leaving the space to find better solutions in the future.

About the data related to the interventional procedure complications of LAAC, they occur mostly in the periprocedure period and decrease in time and with operator experience, which is the opposite of what occurs in the control group with warfarin prescription, which

rate remains constant over time[73]. The periprocedure complications rate highlights the risk of an invasive procedure, and also sets out the importance of time for the balance risk-benefit of this approach. Patient selection is mandatory and the patients with very high risk of stroke and bleeding, with a sufficient life expectancy to profit from LAAC, are the ones considered to benefit the most from these techniques, avoiding long-term anticoagulation. Therefore, patients with many co-morbidities and limited life expectancy may not expect great benefit from this technique, given it's time dependent[59]. Due to the lack of prospective trials, the net clinical benefit of LAAC is not established yet, especially in this particular subset of patients. To point out that LAAC isn't meant to take over oral anticoagulant therapy has the first-line of treatment in non-valvular AF. It is rather an alternative to be proposed in cases where anticoagulation cannot be tolerated.

Another important topic is the variety of protocols adopted in these studies, especially regarding the post-procedure therapy, making it very hard to take further conclusions about the pharmacological regimens to apply after device implantation (Table 5).

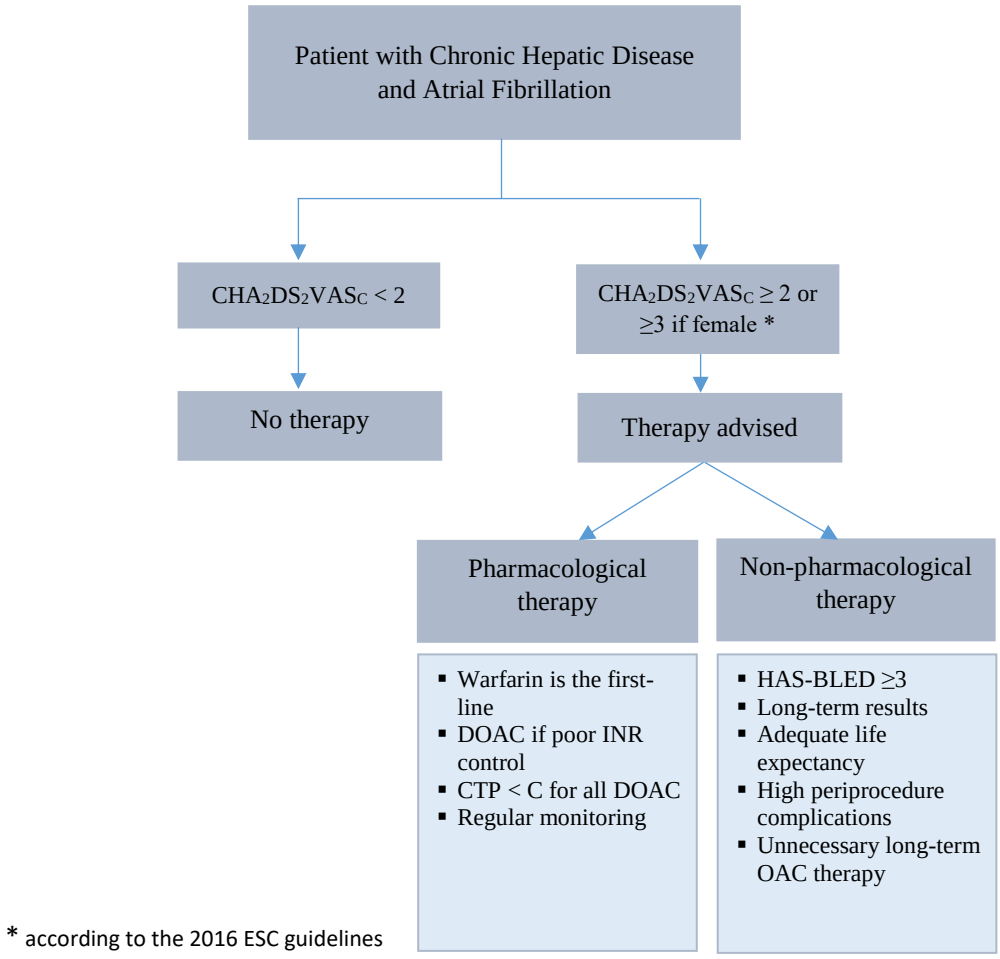

Figure 2 – Algorithm proposed for patients evaluation and therapeutical options

These findings suggest that investments should be made to improve the implantation technique and on the post-procedure protocol, developing more uniform inclusion criteria, including patients at both high risk for stroke and bleeding, justifying the concern to use OACs, in order to reduce periprocedure complication events. Eventually it should be considered a protocol with less intensive post-procedure antithrombotic therapy regimes.

6 | Conclusions

Healthcare professionals have several pharmacological and non-pharmacological options for stroke prophylaxis, but no guidelines exist to guarantee the best treatment to provide to their patients. Selection must be based on the evaluation of the potential risks and the potential benefits of each approach. The appropriate method depends on patient's clinical factors such as tolerability to oral anticoagulants and adherence, risk for bleeding, comorbidities like renal insufficiency or liver impairment, concomitant medications, age and life expectancy, patient's own expectancies and wishes. It is mandatory to take into account all these factors before choosing the best treatment to apply.

About what's the best option for each patient, further studies are required, aimed at the identification of the best method for which patient, and for that direct comparisons between the different methods available are crucial. Until now, it's not possible to claim superiority of one NOAC agent over the other. Although NOACs offer several advantages over warfarin, their safety isn't well proven yet for patients with chronic hepatic disease.

Comparisons should be made also with the different LAAC techniques, and the different anticoagulant options.

Another topic to be addressed by future clinical studies is the need for long-term or indefinite antithrombotic therapy after implantation of an LAA occlusion device.

The relevance of this subject is evidenced by the growing number of older persons and the prevalence of multiple chronic morbidities, such as atrial fibrillation and chronic hepatic disease, in a part due to more sedentarism and obesity.

In the future, it's undeniable that more large, well-designed trials, involving the different devices and comparing them with the different OAC possibilities are required, to ensure the efficacy and safety of all these approaches and to allow further conclusions on which is the more appropriate option for patients with atrial fibrillation and chronic hepatic disease.

7 | Limitations

In this review, we included different types of studies: randomized trials, cohorts, registries, with a mix of prospective and retrospective trials, with different populations, not all limited to patients with chronic liver disease, due to the insufficient studies published in these circumstances, which obliged a change in the inclusion criteria during the research process on the databases.

8 | Conflict of interest

The authors declare they have no conflicts of interest concerning this article.

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